volved repeated surgical intervention anw has been complicated by the development of fistula.

Defects of Other Systems.—Choanal atresia or stenosis was found in three survivors and must be attributed to thalidomide. Cleft palate was present in two children who died in the neonatal period.

Discussion

The defects of thalidomide children conform in most cases to a clearly defined pattern. The upper limb defects may be difficult to distinguish from the Holt-Oram syndrome, but in that condition the legs are normal and there is usually a family history suggesting dominant inheritance. In thalidomide children the thumb is involved first, then the radius, the humerus, and the ulna in that order. The digits are normal or reduced in number, the reduction taking place from the radial to the ulnar side. Digit number is nearly always reduced if there is radial aplasia or hypoplasia, in contrast to the syndrome of radial aplasia with thrombocytopenia, in which there are always five digits. Apart from vestigial supernumerary digits in a few cases extra digits are never present. The radius and ulna may be fused in part or the whole of their length. Less commonly the humerus and ulna may be fused. Every gradation is seen between a normal arm and complete amelia.

By contrast the defects of the leg are very much more "all or nothing." Minor defects are uncommon. The limb is involved proximodistally from congenital dislocation of the hip through femoral hypoplasia to defects of the tibia and fibula. Club-foot is usually associated with tibial defects. The number of toes is normal or increased; there may be seven or eight toes on each foot.

The defects of both upper and lower limbs are usually symmetrical, differing only in detail, but in a few children in this series with asymmetrical or even unilateral limb defects it seemed probable that thalidomide was responsible.

Defects of the ears are usually bilateral but often asymmetrical. The more severe the defect of the pinna the more likely are deafness and facial palsy to be associated. Partial or complete external ophthalmoplegia was seen only in association with ipsilateral facial palsy.

Defects of the eyes may be unilateral or bilateral and are usually asymmetrical. The least defect is coloboma, which may involve only the iris or the retina as well. Microphthalmos is more serious and anophthalmia the most serious eye defect.

Visceral defects, especially of the heart, bowels, and kidneys, were responsible for much of the high perinatal mortality rate and affect many survivors.

The assessment of disability is a difficult enough task at the best of times. The wide variation in the severity of limb defects in thalidomide children, and the great variety of defects involving other systems, leads to a spectrum of disability from incapacitating to negligible. The total disability is not necessarily derived from the sum of independent defects. For example, loss of spinal mobility is more important to the child with no arms than to the child with no legs. Sensory handicaps (deafness and blindness) are more disabling for a child with no hands than to a child who can explore by touch.

There would be little disagreement that the most severe of all handicaps is to be dependent on the help of others for the basic activities of life—feeding, toilet, and dressing. But if this much independence can be achieved is it more disabling to be excluded from competitive games, to have reduced prospects of matrimony, or to be unable to scratch when you itch?

Although there is an obvious relationship between structure and function the functional disability cannot be accurately deduced from knowledge of the structural defect. For example, among the 60 children with upper limb phocomelia and normal legs there was a very wide variation in the degree of independence achieved. Within this group function depends less on minor differences of structure than on the availability of expert guidance from the earliest days, the enthusiasm and ingenuity of the parents, the helpfulness of teachers, and the intelligence and determination of the children themselves.

Sixty of these children were examined in co-operation with Dr. E. P. Quibell, medical director of Chailey Heritage Craft School and Hospital, Sussex. I am grateful to him for valuable discussion of these cases and for his helpful comments.

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MEDICAL MEMORANDA

Central-core Disease and Malignant Hyperpyrexia

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Histochemical and electronmicroscopical studies of muscle showed the characteristic appearances of central-core disease in a patient susceptible to malignant hyperpyrexia—an often fatal complication of general anaesthesia characterized by a steep rise in body temperature, which occurs in patients with an underlying myopathy.

The present paper describes a histological study of muscle in a susceptible patient whose clinical features have been described previously (Denborough *et al.*, 1970).

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Case Report

A 71-year-old paternal aunt of the propositus in a family in which there have been 10 deaths due to malignant hyperpyrexia had shown features of a myopathy since childhood. She did not walk till nearly 3 years of age, has always had a waddling gait, and has evidence of muscle wasting—particularly in the lower parts of the thighs. The myopathy is more noticeable in her than in other affected members of her family. The opportunity to make a detailed histological examination of her muscle arose when she had an operation for removal of a dermoid cyst and fibroids under spinal anaesthesia.

METHODS

A biopsy specimen was taken from the rectus abdominis muscle with the patient's consent.

For histochemistry the muscle was frozen in isopentane precooled in liquid nitrogen, and cryostat sections cut at—16°C were processed for a variety of stains including nicotinamide adenosine diaphorase-tetrazolium reductase, succinic dehydrogenase, lactate dehydrogenase, myofibrillar adenosine triphosphatase, and phosphorylase. The muscle was also processed for electronmicroscopy.

RESULTS

The most striking abnormality was seen in the enzyme histochemical preparations for nicotinamide adenosine diaphorase-tetrazolium reductase, lactate dehydrogenase, and succinic dehydrogenase, in which there were cores in 55% of type 1 fibres (Figs. 1 and 2). All reactions which showed fibre types showed a random chequerboard staining pattern with some type 1 atrophy and no evidence of type grouping. A fibre type count showed 53% type 1 fibres and 47% type 2 fibres.

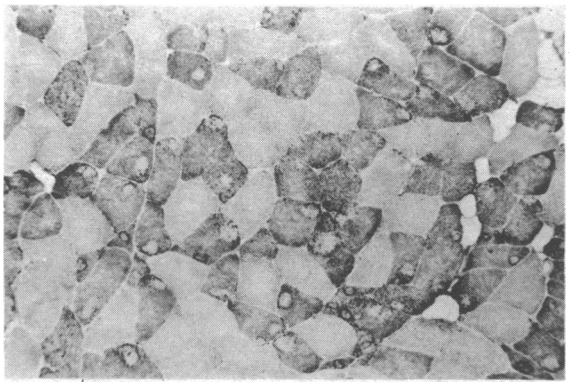

FIG. 1—Histochemical appearance of rectus abdominis muscle. Dark staining fibres are type 1, light staining fibres are type 2. Cores are seen which are present only in type 1 fibres. (Nicotinamide adenosine diaphorase-tetrazolium reductase. ×125.)

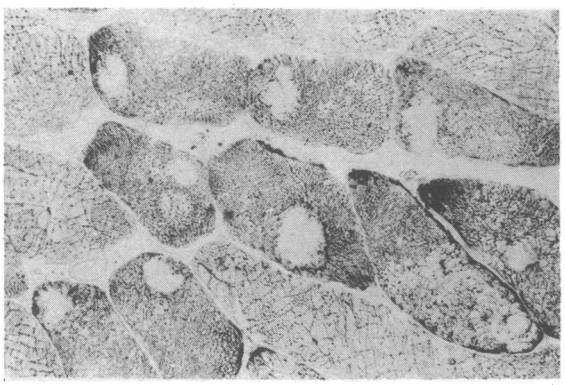

FIG. 2—Histochemical appearance of rectus abdominis muscle. Darker fibres are type 1 and all contain a non-staining core. Several of these cores are sharply demarcated, others are more irregular in outline (Nicotinamide adenosine diaphorase-tetrazolium reductase. ×480.)

Cryostat sections stained with haematoxylin and eosin showed a variation in fibre size with some atrophic fibres. In each muscle bundle a few atrophic fibres were arranged in a group. No regenerating fibres were seen. The fibres ranged in size from 15-95μ. Central nuclei were relatively common, being present in 28% of fibres. There was a mild increase in endomysial connective tissue. Vessels appeared normal and no inflammatory cells were associated with them. A single small collection of mononuclear cells was seen surrounding several muscle fibres, but no phagocytosis was seen and the fibres were intact. No nerves or muscle spindles were present. The features were myopathic and consistent with central-core disease.

Electronmicroscopy confirmed the presence of cores, in which mitochondria were either absent or greatly decreased in number. In these cores triads were present and glycogen was abundant. Several fibres contained tubular structures lying under the plasma membrane. Streaming of the Z-lines was present both in cores and in other parts of the muscle fibres, and distended mitochondria and collections of irregularly-shaped electron-dense material suggestive of target fibres were also seen.

Comment

The striking histological abnormality in this patient who is susceptible to malignant hyperpyrexia is the presence of cores in 55% of her type 1 muscle fibres. This histological appearance in a myopathy has been called central-core disease (Shy and Magee, 1956; Dubowitz and Pearse, 1960).

This is the first characteristic histochemical and electronmicroscopical abnormality to be found in muscle diseases associated with malignant hyperpyrexia in man, although we have recently noted core-like structures in some Landrace pigs, which may also develop this complication of anaesthesia. At least three different clinical types of myopathy have been found in association with malignant hyperpyrexia (King *et al.*, 1972), and it will be of interest to determine whether a similar histological appearance is present in each of the myopathies concerned. The myopathy in the present patient is inherited as a mendelian dominant, and the patient is the most severely affected in her family, so that similar histological abnormalities in her affected relatives may be more difficult to find.

In one congenital myopathy associated with malignant hyperpyrexia in young boys (King *et al.*, 1972) the affected persons have a number of physical abnormalities, and it is of interest to note that some of these physical characteristics such as ptosis, lordosis, and winging of the scapulae have also been described in two children with multicore disease (Engel *et al.*, 1971). In multicore disease multiple randomly distributed short cores were present in both type 1 and type 2 fibres, but the relation between this condition and central-core disease is still uncertain.

It seems likely that the primary biochemical abnormality in malignant hyperpyrexia is a high calcium ion concentration in the myoplasm, which may well be due to a defect in the sarcoplasmic reticulum. In view of this it is interesting to note the unusual tubular structures, which probably represent sarcoplasmic reticulum, in the muscle fibres on electronmicroscopy in the present patient.

An in-vitro study of the muscle from this patient showed a markedly abnormal response to halothane (Moulds and Denborough, 1972), but the relation between the biochemical abnormality in the muscle in malignant hyperpyrexia and the histological appearance of cores in the muscle fibre is still to be defined.

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